REMARKS

Applicants acknowledge that Applicants' Amendment After Final filed May 28, 2004 has been entered. In the absence of any statement to the contrary, it is Applicants' understanding that amended Figures 15A-B and 16A-D, which were submitted in the above-referenced Amendment After Final have been found acceptable by the Official Draftsperson.

I. Request to Change Attorney Docket Number:

Applicants request that the Attorney Docket No. for the above-referenced application be corrected from 9725-005 to **289550-122US2**.

II. Amendments to the Specification:

The specification has been amended to correct minor typographical errors and to delete hyperlinks. In addition, the abstract has been amended to be in compliance with 37 C.F.R. § 1.72(b). No new matter has been added by way of these amendments.

Upon entry of the instant amendments to the specification, Applicants respectfully contend that the objections raised in the Office Action (*see*, Office Action, page 2, sections 5 and 6) have been overcome. Accordingly, Applicants request that these objections be withdrawn.

III. Amendments to the Claims:

Claims 10-13, 18-20 and 22-39 were pending in this application.

Claims 10, 12-13, 18, 22, 27, 30, 32-33 and 36 have been amended without prejudice or disclaimer of the subject matter of these claims. Applicants reserve the right to pursue the claims prior to the instant amendment in future applications. No new matter has been introduced into the application by way of these amendments to the claims. Support for the amendment to claims 10, 18, and 30 can be found *inter alia* at page 18, lines 8-15; and page 58, line 33 to page 60, line 10. Support for the amendment to claims 12 and 32 can be found *inter alia* at the paragraph bridging pages 10-11; page 17, lines 24-31; and page 60, line 15 to page 61,

line 16. Support for the amendment to claims 13, 22, 27, 33 and 36, can be found *inter alia* in the originally filed claims; at page 18, lines 22-31; and page 26, line 11 to page 27, line 17.

Accordingly, upon entry of the instant amendment, claims 10-13, 18-20, and 22-39 are pending in this application.

IV. Withdrawal of Prior Rejections:

Applicants gratefully note that the prior rejections under 35 U.S.C. § 102(b) over Aeschbach *et al.* and Brown *et al.* have been withdrawn in light of Applicants' arguments in the Amendment After Final filed May 28, 2004.

V. Rejections under 35 U.S.C. § 112, first paragraph, enablement:

Claims 10-13 and 22-39 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification.

Summary of Examiner's Arguments:

The Office Action alleged that the specification while being enabling for an isolated stabilized lipase B of *Candida antartica* 'CALB' and subtilisin E comprising at least one di-tyrosine cross-link, wherein at least one tyrosine of a di-tyrosine cross-link originates from a point mutation to tyrosine, and wherein the cross-linked protein retains original function, does not reasonably provide enablement for any isolated protein with said modifications (*see*, Office Action, page 3, section 7). The Office Action further purports that no specific examples other than CALB or subtilisin E are outlined in the specification that teach or provide guidance for stabilizing any protein subjected to point mutation and cross-linking tyrosine residues, or a method of obtaining such a cross-linked protein, wherein the protein is a hormone, a growth factor, a receptor, an enzyme or an antibody (*see*, Office Action, page 5, first full paragraph, emphasis in original). The Examiner alleges that there is no common strategy that can be employed to all or any protein based upon two examples, viz., CALB and subtilisin E, and that

every protein will have to be optimized with respect to the introduction of the tyrosine by point mutation, conditions for cross-linking and with respect to stabilization of the desired function (*see,* Office Action, page 5, second full paragraph).

Applicants' Response:

Applicants respectfully traverse this rejection and assert that the Office Action has not made a *prima facie* case of non-enablement.

According to MPEP § 2164, the purpose of the enablement requirement is that the specification describe the invention in such terms that one skilled in the art can make and use the claimed invention so as to ensure that the invention is communicated to the interested public in a meaningful way. For the reasons presented below, Applicants respectfully assert that the claimed invention is fully enabled.

As a preliminary matter, Applicants point out that the three independent claims of the instant application namely, claims 10, 18 and 30, have been amended. Specifically, claims 10 and 30 have been amended to recite, in relevant part, "An isolated stabilized protein *having a functional activity selected from the group consisting of an enzymatic activity, an antigen-binding activity, a protein-protein interaction activity, a DNA binding activity, a hormone activity, a receptor activity, a growth factor activity, and any combinations thereof...*" whereas claim 18 has been amended to recite, in relevant part, "A method for making a stabilized protein, *wherein the protein has a functional activity selected from the group consisting of an enzymatic activity, an antigen-binding activity, a protein-protein interaction activity, a DNA binding activity, a hormone activity, a receptor activity, a growth factor activity, and any combinations thereof...*" Thus, upon entry of the instant claims, the claims of the instant application will no longer be directed to *ANY* protein, but rather a protein with a specified function. More specifically, the claims will be directed to proteins having a functional activity selected from the group consisting of an enzymatic activity, an antigen-binding activity, a protein-protein interaction activity, a DNA binding activity, a hormone activity, a receptor activity, a growth factor activity, and any combinations thereof. Importantly, each of these functional activities can be readily assayed to determine whether a di-tyrosine cross-linked protein, wherein at least one tyrosine of the di-tyrosine

crosslink originates from a point mutation to tyrosine, retains at least one of the functions displayed by the protein in the absence of di-tyrosine cross-linking.

Second, in response to the Office Action's allegation that no specific examples other than CALB or subtilisin E are outlined in the specification that teach or provide guidance to the ordinarily skilled artisan to achieve Applicants' claimed invention, Applicants respectfully call the Examiner's attention to Example I (Section 6 of the application), starting at page 67 of the application, and the Detailed Description of the Invention (Section 5 of the application), starting at page 17 of the application.

Example I clearly describes how the claimed invention can be applied to an additional class of proteins namely, Fv fragments. Fv fragments consist of the variable regions of the immunoglobulin heavy and light chains, and are among the smallest fragments of immunoglobulin complexes shown to bind antigen. In this example (as opposed to the examples describing CALB and subtlisin E), several Fv fragments are examined through the evaluation of their primary, secondary, tertiary, and quarternary structures. The statistical approach described in detail in this example sheds light on the sensitivities of the structural features of the Fv fragment family, and provides the information required to identify a set of residue pairs that allows stabilization of any Fv fragment through application of the described technology.

In addition to Example I, the Detailed Description of the Invention (Section 5, starting at page 17 of the application) provides considerable guidance to the ordinarily skilled artisan to practice the technology described in the instant application. This section of the application provides a clear and thorough description of the individual steps required to apply the technology to stabilize an isolated protein having a functional activity selected from the group consisting of an enzymatic activity, an antigen-binding activity, a protein-protein interaction activity, a DNA binding activity, a hormone activity, a receptor activity, a growth factor activity, and any combinations thereof, wherein the di-tyrosine cross-linked protein retains at least one functional activity of the un-di-tyrosine cross-linked protein (*see*, Section 5.2, "Application of the Stabilization Technology," starting at page 22). Furthermore, a section on

trouble shooting includes methods for improving the outcome of the application of the technology disclosed in the instant application, should testing reveal unsatisfactory results (*see*, Section 5.17, "Troubleshooting," starting at page 62).

Section 5 describes that the application of the technology to any and all proteins falls broadly into five parts:

I. Reagents and Structural Information: application of the technology may initially be facilitated by obtaining reagents that enable a molecular biological approach, and require obtaining structural information needed to target the DT bonds.

II. Targeting: identification of optimal sites in the structure of a protein or protein complex for targeting/placement of DT bonds.

III. Molecular biological preparation of uncross-linked protein: introduction of point mutations in the gene(s) of the protein or protein complex to direct expression of tyrosine at desired locations (and phenylalanine where an undesirable DT bond may form), and recombinant expression.

IV. DT Cross-linking and Protein Purification: optimizing cross-linking reaction conditions to minimize undesired protein oxidation; cross-linking and purification of cross-linked protein/protein complexes.

V. Testing: analysis of proteins' and protein complexes' gained stability and retained function (before and) following cross-linking.

Each of these steps is described in detail in Section 5 of the application, and is fully enabled.

Specifically, Step I, which comprises obtaining such reagents and structural information on a protein is described in detail in Section 5.4 ("Obtaining Polypeptides to be Stabilized," page 27, line 35 to page 32, line 4).

Having obtained the protein, structural analysis allows identification of sites within the structure of a protein that are suitable for DT cross-linking (Step II). The criteria of what is a 'suitable site' for DT cross-linking is described in detail in Section 5.5 ("Suitable Residues for a Cross-linking Reaction," page 32, line 6 to page 34, line 32). The relationship between structure and function is examined with regard to application of the invention in Section 5.6.1

("Relationship between Structure and Function," page 33, line 27 to page 34, line 22). The process that identifies suitable sites within the structures of proteins and protein complexes is described in subsequent sections. The process essentially applies a set of filters that eliminate amino acid residue pairs in the structures of proteins and protein complexes. These filters eliminate residue pairs that upon point mutation would either distort the structure of proteins and protein complexes, or thereby impair or alter their activity and/or specificity, or not lead to stabilizing DT bond formation within protein structures under cross-linking conditions. This is described in detail in Section 5.9 ("Selection Process," page 41, line 19 to page 46, line 3), and Section 5.10 ("The Filters," page 46, line 5 to page 50, line 30). Residue pairs are selected (or retained in the filters) according to a selection process that applies selection criteria (Section 5.9.1, "Selection Criteria for Amino Acid Substitution", page 41, line 20 to page 43, line 31) that are based on the physical chemical nature of tyrosyl side-chains and DT bonds (Section 5.9.2, "Determination of the Alpha Carbon Distance in the Tyrosyl-Tyrosyl Bond", page 44, lines 1 to 36; and Section 5.9.3 "Calculation of Side-chain Angles in the Tyrosyl Bond", page 45, line 1 to page 46, line 3). Where sufficient data is available, statistical analysis of related proteins can be employed to identify residues that are conserved (by sequence and/or structurally), and that are hence not suitable for point mutation. Such statistical analyses are based on sequence (2-D data) and/or structural data (3-D data). These analyses are described in detail in Section 5.7 ("Statistical Selection Method," page 35, line 1 to page 36, line 23) and Section 5.8 ("Generation and Use of Databases," page 36, line26 to page 41, line 16). Furthermore, to reduce experimentation requirements, computational analysis can be employed to identify where in the structure of a protein or protein complex the DT bond is most likely to introduce a desirable degree of stability while maintaining the functionality (activity and/or specificity) of a protein (Section 5.10.1, "Incorporating Data Derived from Modeling," page 50, lines 5-14). The selection process described above yields a set of residue pairs for further analysis that can vary in size, depending on the stringency by which the Selection Criteria are set. One practicing the present invention would adjust the size of the set of residue pairs selected for further experimentation

based on the sensitivity of the individual protein or protein complex's structure and/or function (activity and/or specificity), the value of the product, and any other such criteria.

Step III relates to the molecular biological preparation of uncross-linked protein. This step is divided into several sub-steps including: (i) preparation of the gene(s) in suitable expansion or expression vectors for point mutation and protein expression; (ii) point mutation (*e.g.*, to phenylalanine) of one of the tyrosyl residues of any tyrosyl pairs identified as a part of the structural analysis of the protein or protein complex, if any, that could or would form an undesirable DT bonds within the structure of the target protein or protein complex; (iii) expression and purification of the above constructs; (iv) testing of the above constructs to ensure that, and/or identify conditions under which, no undesirable DT bonds are formed; (v) point mutation to tyrosine of at least one residue of the selected residue pairs (mutation to tyrosine of both residues if a tyrosyl side chain is not already present at one of the residues of the selected pairs); and (vi) expression and purification of the uncross-linked point mutant protein. Each of these sub-steps is described in the application as filed (*see*, Section 5.11, "DNA Vector Constructs," page 50, line 32 to page 53, line 2; Section 5.13.1, "Introduction of Point Mutations to Phenylalanine", page 54, line 31 to page 55, line 17; Section 5.12, "Systems of Gene Expression and Protein Purification", page 53, line 5 to page 54, line 26; Section 5.13.2, "Purification of Gene Products", page 55, lines 20-30; Section 5.13.3, "The Reaction", page 55, line 33 to page 57, line 11; Section 5.5.3, "Introducing Reactive Side-chains", page 33, lines 11-23; Section 5.13.1, "Introduction of Point Mutations to Phenylalanine", page 54, line 31 to page 55, line 17; Section 5.12, "Systems of Gene Expression and Protein Purification", page 53, line 5 to page 54, line 26; and Section 5.14.1, "Point Mutation to Tyrosine and Gene Product Purification", page 57, lines 15-21).

Step IV consists of two steps: (i) optimization of the chemical reaction conditions leading to the formation of stabilizing DT bonds within the structures of proteins and protein complexes, and cross-linking of a protein or protein complex preparation; and (ii) purification of cross-linked proteins or protein complexes. Optimization of the chemical reaction conditions is carried out for the identification of conditions under which protein constructs with point

mutations removing undesirable tyrosyl side-chains do not form DT bonds (see, Section 5.13.3, "The Reaction", page 55, line 33 to page 57, line 11). Optimization is geared toward minimization of the reaction's strength to minimize undesired oxidation of the protein, as described in Section 5.14.2, "Cross-linking the Polypeptide or Complex", page 57, line 24 to page 58, line 9. After di-tyrosine cross-linking the protein, purification of the cross-linked protein constructs is done as described in the application in Section 5.15, "Purification of Cross-linked Complexes" (page 58, lines 11-27).

Step V involves testing the functional activity and stability of a di-tyrosine cross-linked protein. The availability of a functional assay for the target protein is a pre-requisite for application of this part of the technology's process. Such assays may range from *in vitro* assays, for example of an enzyme, to biological assays, for example of a cytokine, as described in Section 5.16.1, "Retained Function," sub-section "Functionality," at page 59, lines 1-32. The function of a protein is also determined by its specificity, and thus appropriate assays may be applied to determine whether or how application of the present invention affected or altered the specificity of the polypeptide, protein, or protein complex. Such assays are described in Section 5.16.1, "Retained Function," sub-section "Specificity," in the paragraph bridging pages 59-60. In addition to the functional assays described above, the stability of the protein can be tested as described in Section 5.16.2, "Stability" (page 60, line 15 to page 61, line 16). A stabilized protein's pharmacokinetics and therapeutic utility can also be tested in model animal studies (and in patients) as described in Section 5.16.3, "Biodistribution", page 61, lines 19-31; and Section 5.16.4, "Animal and Clinical Studies", page 61, line 34 to page 62, line 7.

Because it may be difficult to accurately predict the effects of point mutations and the introduction of other structural features such as cross-links on protein structure and function, the application further provides methods to improve upon the outcome of the practice of the technology described above to stabilize a polypeptide, protein, or protein complex. In particular, the application provides for methods to troubleshoot when the target polypeptide, protein, or protein complex does not cross-link (Section 5.17.1, "Polypeptide or Complex not Cross-linked", page 62, line 10 to page 63, line 29) and when its functionality is compromised as

determined by post-cross-linking testing (Section 5.17.2, "Compromised Functionality of Polypeptide or Complex", page 63, line 31 to page 64, line 27). Specifically, methods to troubleshoot each of the above problems include adjusting the reaction conditions (reagent concentrations, temperature, pH, etc.), identifying second site mutations to alleviate the problem, directing the cross-link to an alternative residue pair (*e.g.*, by adjusting the selection criteria), and/or any combination thereof.

In summary, because the Detailed Description of the Invention (discussed above) in combination with Examples I, II and III of the instant application provide more than adequate guidance to one of ordinary skill in the art to practice the invention as claimed, Applicants respectfully contend that the application as filed is fully enabled.

To further support Applicants' position that the application as filed is fully enabling for the claimed invention, Applicants also provide herewith a Declaration under 37 C.F.R. § 1.132 by Christopher P. Marshall, Ph.D. (*see*, Appendix A). In the Declaration, Dr. Marshall provides data to show that when subtilisin E is di-tyrosine cross-linked according to the guidance provided in the instant application, subtilisin E retains functional activity and is more stable than a subtilisin E protein that has not been di-tyrosine cross-linked. Accordingly, Applicants respectfully contend that one of ordinary skill in the art can achieve Applicants' claimed invention by following the steps disclosed in the instant application.

Applicants would like to remind the Examiner that the Federal Circuit has made clear that an applicant need not have actually reduced an invention to practice prior to filing (*see, In Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987). Furthermore, the Court of Customs and Patent Appeals and Interferences (CCPA) has also held that a specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*see, In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). In the instant application, Applicants have not only provided three examples, but also provided considerable guidance in the Detailed Description of the Invention to enable one of ordinary skill in the art to practice the claimed invention.

The CCPA has also held that the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Thus, the court has acknowledged that some experimentation is permissible. Furthermore, the Federal Circuit has clarified that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). MPEP § 2164.01(a) states that there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). MPEP § 2164.05 states that the examiner must weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The determination should always be based on the weight of all the evidence. Applicants respectfully assert that although experimentation may be necessary to practice the claimed invention, the experimentation required is not undue. This is supported by the data in the Declaration of Dr. Marshall, showing that subtilisin E prepared according to the guidance in the instant application, both retains at least one function of the uncross-linked protein, and has increased stability. Thus, in light of the detailed guidance in the specification, the three examples provided in the application, and the Declaration by Dr. Marshall included herewith, Applicants respectfully aver that the totality of evidence indicates that Applicants have enabled the invention as claimed.

Finally, with respect to the enablement rejection relating to "fragments," (*see*, Office Action, page 5, lines 6-9), Applicants note that the claims in question are dependent claims of a parent claim that requires that "the di-tyrosine cross-linked protein retains at least one function displayed by the protein in the absence of di-tyrosine crosslinking." Accordingly, the issue raised in the Office Action of a 2-amino acid fragment not retaining any functionality of the original protein is moot.

For the foregoing reasons, Applicants assert that the claimed invention in the instant application is fully enabled. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph (enablement), be reconsidered and withdrawn.

VI. Rejections under 35 U.S.C. § 112, first paragraph, written description

The Office Action rejected claims 10-13 and 22-39 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention (*see*, Office Action, page 6, section 8).

Summary of Examiner's Argument:

The Examiner alleged that the specification only provides two representative species (CALB and subtilisin E) that fall under the genus of "an isolated protein." In addition the Examiner purports that the specification fails to describe additional representative species of the proteins for which no predictability of function is apparent. The Examiner concludes that given this lack of additional representative species, such as the numerous proteins with no defined activity, or function, or name, Applicants have not sufficiently described the claimed invention.

Applicants' Response:

Applicants respectfully traverse this rejection for the reasons presented below.

As stated above, and repeated here for the Examiner's convenience, Applicants note that the three independent claims of the instant application namely, claims 10, 18 and 30, have been amended. Specifically, claims 10 and 30 have been amended to recite, in relevant part, "An isolated stabilized protein *having a functional activity selected from the group consisting of an*

enzymatic activity, an antigen-binding activity, a protein-protein interaction activity, a DNA binding activity, a hormone activity, a receptor activity, a growth factor activity, and any combinations thereof..." whereas claim 18 has been amended to recite, in relevant part, "A method for making a stabilized protein, *wherein the protein has a functional activity selected from the group consisting of an enzymatic activity, an antigen-binding activity, a protein-protein interaction activity, a DNA binding activity, a hormone activity, a receptor activity, a growth factor activity, and any combinations thereof...*" Thus, upon entry of the instant claims, the claims of the instant application will no longer be directed to *ANY* protein, but rather, to a protein with a specified function. More specifically, the claims will be directed to proteins having a functional activity selected from the group consisting of an enzymatic activity, an antigen-binding activity, a protein-protein interaction activity, a DNA binding activity, a hormone activity, a receptor activity, a growth factor activity, and any combinations thereof. Importantly, each of these functional activities can be readily assayed to determine whether a di-tyrosine cross-linked protein, wherein at least one tyrosine of the di-tyrosine crosslink originates from a point mutation to tyrosine, retains at least one of the functions displayed by the protein in the absence of di-tyrosine cross-linking.

In addition, as discussed above, the Examiner's attention is drawn to the fact the application as filed has three, not two, examples. In addition to CALB and subtilisin E, the application also provides an example directed to stabilization of Fv fragments (Example I). Furthermore, the specification provides considerable guidance on additional representative species of proteins that can be used to practice the claimed invention (*see*, for example, Sections 5.2.1, 5.2.2 and 5.3 of the application). Also, as described in great detail in the section relating to the enablement rejection (*see*, above), Applicants have pointed to the substantial written description guidance presented in the specification with respect to practicing the claimed invention.

For the foregoing reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph (written description), be reconsidered and withdrawn.

VII. Rejections under 35 U.S.C. § 112, second paragraph:

Claims 18-20, and 30-39 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite (*see*, Office Action, pages 7-8, section 9).

Claims 20 and 35 were alleged to be indefinite for reciting "wherein cross-linking is catalyzed..." without describing what cross-linking reaction is catalyzed. Applicants call the attention of the Examiner to the language of claims 20 and 35, both of which explicitly recite, in relevant part, "wherein the di-tyrosine crosslinking is catalyzed..." Accordingly, this rejection has been rendered moot.

Claims 36-39 stand rejected for recitation of the phrase: "protein comprises an enzyme, an antibody, or a fragment thereof." Applicants assume that the Examiner also intended to include claim 27 in this rejection since it recites the same language. The Office Action indicated that these claims are indefinite because a protein or chimeric polypeptide comprises amino acid residues and not an enzyme, an antibody or a fragment thereof. Applicants respectfully contend that a chimeric polyeptide can comprise a hormone, an antibody, an enzyme, etc. For example, a Flag-growth hormone chimeric polypeptide comprises a hormone and an epitope tag. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 18-20 and 30-39 stand rejected as allegedly being indefinite for omitting an essential element namely, indicating that the cross-linking the residue pairs occurs in the presence of an oxidant. Without acquiescing to the propriety of this rejection, and solely with a view to expediting prosecution in the above-referenced application, claims 18 and 30 have been amended to recite, in relevant part, " (c) cross-linking residue pairs (or tyrosine residues) in the presence of an oxidant..." In light of the instant amendment to claims 18 and 30, Applicants respectfully contend that this rejection has been rendered moot. In view of the foregoing remarks, Applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection.

CONCLUSION

Claims 10-13, 18-20, and 22-39 are pending in the instant application.

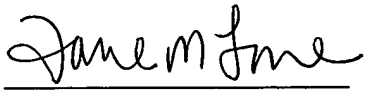
Applicants respectfully submit that the application and claims are now in condition for allowance. If the Examiner believes that further discussion would be helpful, the Examiner is respectfully requested to telephone the undersigned attorney at (212) 937-7233 and is assured of full cooperation to advance the application to allowance.

No fees are believed to be due in connection with this filing; however, if any fees are due, the Commissioner is hereby authorized to charge any fee(s) that may be necessary in this application to Deposit Account No. 08-0219, Order No. 289550-122US2.

Respectfully submitted,

WILMER CUTLER PICKERING
HALE AND DORR LLP

Date: August 31, 2004

By: 

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APPENDIX A

Attached is a copy of a Declaration under 37 C.F.R. § 1.132 by Dr. Christopher P. Marshall.